Arab Republic of Egypt
Egyptian Drug Authority
CAPP

جمهورية مصر العربية
هيئة الدواء المصرية
الإدارة المركزية للمستحضرات الصيدلية

EDA Assessment Report for human medicinal product

(Scientific Discussion)

Recoxitro 60mg, 90mg & 120mg film coated tablets

(Etoricoxib)

Date: October 2023

I. Introduction

- Based on the review of the quality, safety and efficacy data, the Egyptian Drug Authority have granted marketing authorization for Recoxitro 60mg, 90mg & 120mg film coated tablets from Marcyrl Pharmaceutical Industries.

- The product contains the active substance "Etoricoxib" which belongs to a group of medicines called "Selective COX-2 inhibitors". These belong to a family of medicines called non-steroidal anti-inflammatory drugs (NSAIDs). It is indicated in adults and adolescents 16 years of age and older for the symptomatic relief of osteoarthritis (OA), rheumatoid arthritis (RA) ankylosing spondylitis and the pain and signs of inflammation associated with acute gouty arthritis and the short-term treatment of moderate pain after dental surgery.

II. Quality Aspect

Drug Substance

- An APIMF (Applicant/ restricted part) has been submitted for evaluation.

- The drug substance is an off - white to creamish colored powder slightly hygroscopic. It is soluble in methanol, in chloroform, in methylene chloride and in acetone. Etoricoxib exhibits polymorphism.

- The synthesis of drug substance includes single step to produce Etoricoxib (Wet) which is subjected to drying followed by physical operation(s) and packing. The two starting materials, all reagents and solvents are well controlled.

- The drug substance is elucidated via Elemental analysis, Mass spectroscopy, FTIR, UV Spectroscopy, Nuclear Magnetic Resonance (^{1}H, ^{13}C and DEPT-135) and the structure is well characterized. As polymorphism is an important issue for the drug substance, polymorphic evaluation report (by P-XRD, DSC and TGA) is submitted to prove **Form-I** polymorph.

- The drug substance specifications are in accordance with "In-house" specifications and include the following tests: description, identification (by IR), water content (by Karl Fischer), residue on ignition, assay and related substances (by HPLC) & residual solvents (by GC), microbiological tests, P-XRPD & particle size distribution. all limits are acceptable.

- All analytical procedures were adequately described and well validated.

- The applicant provided batch analysis results of 3 drug substance batches demonstrating compliance with the current drug substance specification.

- The API is packed in white LDPE bag twisted and tied. It is inserted in black LDPE bag twisted and tied (Primary packing). The primary packing material is placed in an HDPE drum (Secondary packing). Container closure system is suitable to store API and comply with food grade packaging material and the specifications are acceptable.

- Stability of API is submitted (accelerated at 40°C±2°C / 75±5%RH and long term at 25°C±2°C / 60±5%RH) and conclude the conformity of specifications during the retest period and storage conditions. The storage conditions for Etoricoxib are "Preserve in well closed, light-resistant containers and Store at 25°C, excursions permitted between 15°C and 30°C".

Medicinal Product

Product Description

- Recoxitro film coated tablets are pale yellow to deep yellow round biconvex film coated tablets (for all strengths).
- The product is packed in Al/Transparent PVC/PVDC strip of 10 film coated tablets.
- The excipients for all strengths are: microcrystalline cellulose, dibasic calcium phosphate anhydrous, copovidone, croscarmellose sodium, magnesium stearate & purified water. Film Coat contains hypromellose 5 mpas, triacetin, titanium dioxide (C.I: 77891), yellow iron oxide (C.I: 77492), polyethylene glycol 4000, talc & purified water.

Pharmaceutical development

- the development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop a product equivalent to the reference product.
- Overall, the choices of the packaging, manufacturing process, compatibility, overage physicochemical properties and microbiological attributes are justified.

Manufacturing process

- The manufacturing process is done by mixing, wet granulation, drying, milling, mixing, lubrication, compression and film coating. *The potential of polymorphic conversion of Etoricoxib during wet granulation was raised by the authority and justification has been submitted.*
- The manufacturing process was adequately validated according to relevant guidelines. Validation included three primary sized batches.

Control of excipients

- All excipients comply with USP except for coloring agents which are in house. The specifications of the excipients are well justified.

Product specification

- Product specification includes the four universal tests for description, identification, assay, impurities and additional tests including mass uniformity, disintegration, dissolution, uniformity of dosage units & microbiological tests. All limits are acceptable.
- Analytical methods were adequately described and well validated.
- Batch Analysis from the proposed production site were provided 3 batches of each strength, demonstrating compliance with the release specification.
- Container closure system is suitable to store finished pharmaceutical product and comply with food grade packaging material and the specifications are acceptable.
- Stability of finished pharmaceutical product is submitted and conclude the conformity of specifications during the shelf life and storage conditions. The storage conditions for the finished pharmaceutical product are "store at temperature not exceeding 30°C, in a dry place".
- There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

Conclusion:
Based on the review of CTD quality module and other supplementary documents; from the quality point, the product is approved.

III. Non-Clinical

No new preclinical data have been submitted with this application. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application. An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

IV. Clinical Aspects

Introduction
Etoricoxib 120mg is well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature.
Etoricoxib is indicated for the treatment of rheumatoid arthritis, chronic low back pain, acute pain, and
Gout. Etoricoxib is an oral, selective cyclo-oxygenase-2 (COX-2) inhibitor within the clinical dose range.

Pharmacokinetics

Bioequivalence Study

The bioequivalence study was conducted on the test product Recoxitro 120mg film coated tablets (Etoricoxib 120mg) manufactured by: Marcyrl Pharmaceutical Industries, relative to the reference product Arcoxia 120mg film coated tablets (Etoricoxib 120mg) produced by: Merck Sharp & Dohme Limited, U.K administered to healthy participants.

Biowaiver

The EDA was granted a biowaiver for the lower strengths Recoxitro 60mg & 90mg film-coated tablets based on the following arguments:

- The qualitative and quantitative composition of the different strengths is the same.
- All strengths of Etoricoxib are manufactured by the same process.
- Etoricoxib has linear pharmacokinetics over the therapeutic dose range.
- All tablets strengths have comparable dissolution profiles according to the provided in vitro dissolution data.

Design

Randomized Single Oral Dose, Open-Label, Two-Treatment, Two-Sequence, Two Period, crossover bioequivalence study with a washout period of two weeks between periods under fasting conditions in healthy participants.

On randomized manner each subject received single oral dose from test & reference products directly into mouth administrated by 240 ml water after overnight fasting (at least 8-10 hours in fasting) according to the randomization sheet.

Blood Sampling: pre-dose blood sample were withdrawn at 0 0.16, 0.33, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 48, 60 and 72. after dosing.

Analytical Methods

All procedures used to perform the bio-analyses of Etoricoxib 120mg in subject samples were executed according to international guidelines and official publications.

CRO developed an adequately validated method to ensure data integrity, Accuracy and Precision of data generated during sampling, sample treatment and bioanalyses. The bioequivalence study accordance with acceptable standards of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range) of **Etoricoxib 120mg** under fast conditions.

Treatment N=28	AUC0-72 (ng.h/ml)	Cmax (ng/ml)	tmax (h)	$T_{1/2}$ (h)
Test	50490.38 ± 15192.83	4182.07 ± 976.04	1.63	20.31±9.79
Reference	49574.31 ± 14233.43	3746.77 ± 1220.51	1.50	21.68±10.84
***Ratio (90%) CI**	101.42% (97 %-106%)	115.86% (107%-125%)	--------	-------

*ln-transformed values

Conclusion

The 90% confidence intervals calculated for C_{max}, AUC $_{0\text{-}t}$ and AUC $_{0\text{-}inf}$ are within the bioequivalence acceptance range of 80 % - 125 %.

Based on this study demonstrated that Etoricoxib 120mg in product dosage form of the test product Recoxitro 120mg film coated tablets manufactured by: Marcyrl pharmaceutical Industries, & the reference product Arcoxia 120 mg film coated tablets (Etoricoxib 120mg) produced by: Merck Sharp & Dohme Limited, UK are bioequivalent after a single oral dose of test and reference administration under fasting conditions on 28 participants.